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Cyanides: Ambient Water Quality Criteria

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CYANIDES

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for cyanides. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi....

KEYWORDS: *Water quality, *Toxicology, *Cyanides, *Toxic substances, *Water pollution effects(Humans).

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CRITERION DOCUMENT

CYANIDE

CRITERIA

Aquatic Life

For free cyanide (expressed as CN) the criterion to protect freshwater aquatic life as derived using the Guidelines is 1.4 ug/l as a 24-hour average and the concentration should not exceed 38 ug/l at any time.

For saltwater aquatic life, no criterion for free cyanide can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of cyanide ingested through water and through contaminated aquatic organisms, the ambient water quality criterion is determined to be 200 ug/l.

Introduction

Cyanide exists in water in the free form (CN^- and HCN) which is extremely toxic or bound to organic or inorganic moieties in which it is less toxic. Free and complex forms of cyanide can be converted one to the other under conditions found in the aquatic environment. The criterion is based on free cyanide, since that is the principle toxic moiety (Broderius, 1979; Smith, et al. 1979; Smith, et al. 1979).

Cyanide is lethal to freshwater fishes at concentrations as low as about 50 µg/l and has been shown to adversely affect invertebrates and fishes at concentrations of about 10 µg/l. Very few saltwater data have been generated.

Because of the volatility of HCN, it tends to escape from the water column. In addition, it is readily degraded by microorganisms and by animal metabolism. For these reasons it is not expected to bioconcentrate in aquatic organisms.

Cyanides are known to be degraded by human liver to the less toxic thiocyanate and despite their high levels of acute toxicity, are not known to be chronically toxic to humans.

REFERENCES

Boderius, S.J., et al. 1977. Relative toxicity of free cyanide and dissolved sulfide forms to the fathead minnow, Pimephales promelas. Jour. Fish. Res. Board (insert). 35: 2323.

Smith, L.L., Jr. et al. 1979. Acute and chronic toxicity of HCN to fish and invertebrates. U.S. Environ. Prot. Agency. Ecological Report Series. EPA-600/3-79-009.

Smith, L.L., et al. 1978. Acute toxicity of hydrogen cyanide to freshwater fishes. Arch. Environ. Contam. Toxicol. 7: 325.

AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Compounds containing the cyanide group (CN) are used and readily formed in many industrial processes and can be found in a variety of effluents, such as those from the steel, petroleum, metal plating, mining, and chemical industries. Cyanide commonly occurs in water as hydrocyanic acid (HCN), the cyanide ion (CN^-), simple cyanides, metallocyanide complexes, or as simple chain and complex ring organic compounds. "Free cyanide" is defined as the sum of the cyanide present as either HCN or CN^-. The alkali metal salts such as potassium cyanide (KCN) and sodium cyanide (NaCN) are very soluble in aqueous solutions and the resulting cyanide ions readily hydrolyze with water to form HCN. The extent of HCN formation is dependent upon temperature and pH. At 20° C and a pH of 8 or below the fraction of free cyanide existing as HCN is at least 0.96.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506-(May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The cyanide ion (CN^-) can combine with various heavy metal ions to form metallocyanide complex anions, whose stability is highly variable. Zinc and cadmium cyanide complexes, when diluted with water, are known to rapidly and nearly completely dissociate to form HCN. Some of the other metallocyanide anions, such as those formed with copper, nickel, and iron, demonstrate varying degrees of stability. The hexacyanoferrate (II) and (III) complexes are subject to direct photolysis by natural light. The release of cyanide ion by this phenomenon may be important in relatively clear receiving waters.

The toxicity to aquatic organisms of most simple cyanides and metallocyanide complexes is due mostly to the presence of HCN as derived from ionization, dissociation, and photodecomposition of cyanide-containing compounds (Doudoroff, 1976; Smith et al., 1979), although the cyanide ion (CN^-) is also toxic (Broderius et al., 1977). In most cases the complex ions themselves have relatively low toxicity. Cyanide affects animals by inhibiting utilization of available oxygen for metabolism at the cellular level of respiration.

Since both HCN and CN^- are toxic to aquatic life and since the vast majority of free cyanide usually exists as the more toxic HCN, and since almost all existing CN^- can be readily converted to HCN at pH values that commonly exist in surface waters, the cyanide criterion will be stated in terms of free cyanide expressed as CN. Free cyanide is a much more reliable index of toxicity than total cyanide since the ratio of free to total may be quite variable in natural waters.

All of the cyanide concentrations given herein are free cyanide expressed as CN. Data reported as µg HCN/l were adjusted to free cyanide as CN as follows:

$$\text{Free cyanide } (\mu g\ CN/l) = \frac{(\mu g\ HCN/l)}{1/(1+10^{pH-pK_{HCN}})} \times \frac{\text{mol.wt. CN}}{\text{mol. wt. HCN}}$$

where $pK_{HCN} = 1.3440 + \frac{2347.2}{T(°K)}$ (Izatt et al., 1962).

Acute Toxicity

In Table 1 the LC50 values based on tests with nine fish species are summarized. The greatest number of tests were conducted with brook trout, bluegill and fathead minnows. Eighty percent of the data resulted from studies conducted by Smith et al. (1978) and Broderius et al. (1977). All of their tests were conducted under flow-through conditions with the reported HCN levels calculated from measured free cyanide concentrations.

Certain life stages and species of fish appear to be more sensitive to cyanide than others. Eggs, sac fry, and warmwater species tended to be the most resistant. A review of pertinent data indicates that free cyanide concentrations in the range from about 50 to 200 µg/l have eventually proven fatal to most species of the more sensitive fish with concentrations much above 200 µg/l being rapidly fatal to most fish species.

A number of authors have reported an increase in toxicity of cyanide with reduction in dissolved oxygen below the 100 percent saturation level. The tolerance of fish to cyanide solutions that are rapidly lethal has been observed to decrease with a rise of temperature. However, long term lethality tests have

demonstrated (Smith et al., 1978) that fish are more susceptable to cyanide with a reduction in temperature. No pronounced relationship has been observed between the acute toxicity of cyanide to fish and alkalinity, hardness, and pH below about 8.3.

When the geometric mean of the acute values is divided by the sensitivity factor (3.9), a Final Fish Acute Value of 38 µg/l is obtained. Since no adjusted values from Table 1 are below this value, the sensitivity factor (from the Guidelines) appears to be slightly conservative. For comparison, the lowest 96 hour LC50 value from a flow-through test with measured concentrations is 52 µg/l (Smith et al. 1978).

The results of 11 acute tests with 6 invertebrate species are given in Table 2. With two exceptions (Oseid and Smith, in press), all results are based on static tests with unmeasured concentrations. The geometric mean of the adjusted values (Table 2) divided by the sensitivity factor (21) gives a Final Invertebrate Acute Value of 60 µg/l. None of the corrected LC50 values are lower than this value. Because the Final Fish Acute Value is lower than the comparable value for invertebrate species, the Final Acute Value is 38 µg/l.

Chronic Toxicity

Results from only a few sublethal and partial life cycle chronic tests with fish have been reported (Table 3). Based on long-term survival from an embryo-larval test with bluegills and reproduction by brook trout and fathead minnows, the geometric

mean of the chronic effects listed in Table 3 is 9.6 µg/l. This value divided by the sensitivity factor (6.7) yields a Final Fish Chronic Value of 1.4 µg/l. This value is about 30 times lower than the Final Fish Acute Value.

Two invertebrate life cycle tests (Table 4) were conducted; one with isopods and the other with the scud, Gammarus pseudolimnaeus. The chronic values were 34.1 and 18.3 µg/l, respectively. When the geometric mean of these two values is divided by the sensitivity factor (5.1), it results in a Final Invertebrate Chronic Value of 4.9 µg/l which is about 14 times lower than the Final Invertebrate Acute Value. Since the Final Fish Chronic Value is lower than the Final Invertebrate Chronic Value, the Final Chronic Value is 1.4 µg/l.

Plant Effects

Only one plant test has been reported (Table 5). According to Fitzgerald et al. (1952) 90 percent of the blue-green alga, Microcystis aerusinoss, was killed when exposed to a free cyanide concentration of 7,790 µg/l. Thus, the Final Plant Value is 7,790 µg/l.

Residues

No residue data were found for cyanide.

Miscellaneous

Table 6 contains no data that would alter the selection of 1.4 µg/l as the Final Chronic Value. In fact, there are some additional studies that are supportive of this value.

Several authors (Neil, 1957; Broderius, 1970; Dixon, 1975; Lesniak, 1977; Leduc, 1978; Oseid and Smith, in press; Ruby and Dixon, manuscript) reported adverse effects due to cyanide at concentrations as low as 10 µg/l. In another study, Kimball et al. (1978) reported that adult bluegills exposed to 5.2 µg/l for 289 days exhibited no reproduction. Thus, the Final Chronic Value of 1.4 µg/l, based on fish chronic data, does not appear to be unrealistic in view of these studies and the results of the invertebrate chronic tests.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

All concentrations herein are for free cyanide expressed as CN. The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 38 µg/l

Final Invertebrate Acute Value = 60 µg/l

Final Acute Value = 38 µg/l

Final Fish Chronic Value = 1.4 µg/l

Final Invertebrate Chronic Value = 4.9 µg/l

Final Plant Value = 7,790 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 1.4 µg/l

0.44 x Final Acute Value = 17 µg/l

The maximum concentration of free cyanide is the Final Acute Value of 38 µg/l and the 24-hour concentration is the Final Chronic Value of 1.4 µg/l. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For free cyanide (expressed as CN) the criterion to protect freshwater aquatic life as derived using the Guidelines is 1.4 µg/l as a 24-hour average and the concentration should not exceed 38 µg/l at any time.

Table 1. Freshwater fish acute values for cyanide

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Brook trout (sac fry), Salvelinus fontinalis	FT	M	96	105	105	Smith, et al. 1978
Brook trout (sac fry), Salvelinus fontinalis	FT	M	96	342	342	Smith, et al. 1978
Brook trout (sac fry), Salvelinus fontinalis	FT	M	96	507	507	Smith, et al. 1978
Brook trout (sac fry), Salvelinus fontinalis	FT	M	96	252	252	Smith, et al. 1978
Brook trout (swim-up), Salvelinus fontinalis	FT	M	96	84	84	Smith, et al. 1978
Brook trout (swim-up), Salvelinus fontinalis	FT	M	96	54.4	54.4	Smith, et al. 1978
Brook trout (swim-up), Salvelinus fontinalis	FT	M	96	86.5	86.5	Smith, et al. 1978
Brook trout (swim-up), Salvelinus fontinalis	FT	M	96	104	104	Smith, et al. 1978
Brook trout (swim-up), Salvelinus fontinalis	FT	M	96	90.3	90.3	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	73.5	73.5	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	83.0	83.0	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	75.0	75.0	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	86.4	86.4	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	91.9	91.9	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	99.0	99.0	Smith, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	96.7	96.7	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	112	112	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	52	52	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	60.2	60.2	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	66.8	66.8	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	71.4	71.4	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	97.0	97.0	Smith, et al. 1978
Brook trout (juvenile), Salvelinus fontinalis	FT	M	96	143	143	Smith, et al. 1978
Brook trout (adult), Salvelinus fontinalis	FT	M	96	156	156	Cardwell, et al. 1976
Rainbow trout, Salmo gairdneri	FT	M	48	68	55	Brown, 1968
Rainbow trout (juvenile), Salmo gairdner	FT	M	96	57	57	Smith, et al. 1978
Goldfish (juvenile), Carassius auratus	FT	M	96	318	318	Cardwell, et al. 1976
Fathead minnow (embryo), Pimephales promelas	FT	M	96	347	347	Smith, et al. 1978
Fathead minnow (embryo), Pimephales promelas	FT	M	96	272	272	Smith, et al. 1978
Fathead minnow (embryo), Pimephales promelas	FT	M	96	201	201	Smith, et al. 1978
Fathead minnow (embryo), Pimephales promelas	FT	M	96	123	123	Smith, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow (embryo), Pimephales promelas	FT	M	96	186	186	Smith, et al. 1978
Fathead minnow (embryo), Pimephales promelas	FT	M	96	200	200	Smith, et al. 1978
Fathead minnow (embryo), Pimephales promelas	FT	M	96	206	206	Smith, et al. 1978
Fathead minnow (fry), Pimephales promelas	FT	M	96	120	120	Smith, et al. 1978
Fathead minnow (fry), Pimephales promelas	FT	M	96	98.7	98.7	Smith, et al. 1978
Fathead minnow (fry), Pimephales promelas	FT	M	96	81.8	81.8	Smith, et al. 1978
Fathead minnow (fry), Pimephales promelas	FT	M	96	110	110	Smith, et al. 1978
Fathead minnow (fry), Pimephales promelas	FT	M	96	116	116	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	119	119	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	126	126	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	81.5	81.5	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	124	124	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	137	137	Smith, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	131	131	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	105	105	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	119	119	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	131	131	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	122	122	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	161	161	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	188	188	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	175	175	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	163	163	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	169	169	Smith, et al. 1978
Fathead minnow (juvenile), Pimephales promelas	S	U	96	230	125.7	Doudoroff, 1956

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	120	120	Broderius, et al. 1977
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	113	113	Broderius, et al. 1977
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	128	128	Broderius, et al. 1977
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	128	128	Broderius, et al. 1977
Fathead minnow, Pimephales promelas	S	M	96	350	248	Henderson, et al. 1961
Fathead minnow, Pimephales promelas	S	M	96	230	163	Henderson, et al. 1961
Fathead minnow, Pimephales promelas	S	M	48	240	138	Black, et al. 1957
Black-nosed dace, Rhinichthys atratulus	FT	M	24	220	145	Lipschuetz & Cooper, 1955
Mosquitofish, Gambusia affinis	S	U	96	639	350	Wallen, et al. 1957
Guppy (adult), Poecilia reticulata	FT	M	96	147	147	Anderson & Weber, 1975
Bluegill (fry), Lepomis macrochirus	FT	M	96	364	364	Smith, et al. 1978
Bluegill (fry), Lepomis macrochirus	FT	M	96	232	232	Smith, et al. 1978
Bluegill (fry), Lepomis macrochirus	FT	M	96	279	279	Smith, et al. 1978
Bluegill (fry), Lepomis macrochirus	FT	M	96	273	273	Smith, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	81	81	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	85.7	85.7	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	74	74	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	100	100	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	107	107	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	99.0	99.0	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	113	113	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	121	121	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	FT	M	96	126	126	Smith, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	S	U	96	180	98	Cairns & Scheier, 1958
Bluegill (adult), Lepomis macrochirus	S	M	48	160	92	Cairns, et al. 1965
Bluegill (juvenile), Lepomis macrochirus	FT	M	48	134	108	Cardwell, et al. 1976
Bluegill (juvenile), Lepomis macrochirus	FT	M	72	154	142	Doudoroff, et al. 1966
Bluegill, Lepomis macrochirus	S	U	96	180	98	Patrick, et al. 1968
Bluegill (juvenile), Lepomis macrochirus	S	U	48	280	124	Turnbull, et al. 1954

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill (juvenile), Lepomis macrochirus	S	M	96	150	106	Henderson, et al. 1961
Bluegill (juvenile), Lepomis macrochirus	S	M	96	160	114	Cairns & Scheier, 1963
Yellow perch (embryo), Perca flavescens	FT	M	96	281	281	Smith, et al. 1978
Yellow perch (fry), Perca flavescens	FT	M	96	288	288	Smith, et al. 1978
Yellow perch (fry), Perca flavescens	FT	M	96	330	330	Smith, et al. 1978
Yellow perch (juvenile), Perca flavescens	FT	M	96	88.9	88.9	Smith, et al. 1978
Yellow perch (juvenile), Perca flavescens	FT	M	96	93	93	Smith, et al. 1978
Yellow perch (juvenile), Perca flavescens	FT	M	96	74.7	74.7	Smith, et al. 1978
Yellow perch (juvenile), Perca flavescens	FT	M	96	94.7	94.7	Smith, et al., 1978
Yellow perch (juvenile), Perca flavescens	FT	M	96	101	101	Smith, et al., 1978
Yellow perch (juvenile), Perca flavescens	FT	M	96	107	107	Smith, et al., 1978

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 147.9 µg/l $\frac{147.9}{3.9}$ = 38 µg/l

Lowest value from a flow-through test with measured concentrations = 52 µg/l

Table 2. Freshwater invertebrate acute values for cyanide

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Snail, *Goniobasis livescens*	S	U	48	760,000	276,800	Cairns, et al. 1976
Snail (embryo), *Lymnaea spp*	S	U	96	51,900	44,000	Dowden & Bennett, 1965
Snail, *Lymnaea emarginata*	S	U	48	3,300	1,202	Cairns, et al. 1976
Snail, *Physa heterostropha*	S	U	96	432	366	Patrick, et al. 1968
Snail, *Physa heterostropha*	S	U	96	431	365	Cairns & Scheier, 1958
Snail, *Physa integra*	S	U	48	1,350	492	Cairns, et al. 1976
Cladoceran, *Daphnia pulex*	S	U	48	83	70	Lee, 1976
Isopod, *Asellus communis*	FT	M	96	2,326	2,326	Oseid & Smith, In press
Scud, *Gammarus pseudolimnaeus*	FT	M	96	167	167	Oseid & Smith, In press
Mayfly, *Stenonema rubrum*	S	U	48	500	182	Roback, 1965
Caddisfly, *Hydropsyche spp*	S	U	48	2,000	728	Roback, 1965

* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 1,252 µg/l $\frac{1,252}{21}$ = 60 µg/l

Lowest value from a flow-through test with measured concentrations = 167 µg/l

Table 3. Freshwater fish chronic values for cyanide

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Reference
Brook trout, *Salvelinus fontinalis*	LC	5.6-11.0	7.9	Koenst, et al. 1977
Fathead minnow, *Pimephales promelas*	LC	13.3-20.2	16.4	Lind, et al. 1977
Bluegill, *Lepomis macrochirus*	E-L	9.3-19.8	6.8	Kimball, et al. 1978

* LC - life cycle or partial life cycle; E-L = embryo-larval test

Geometric mean of chronic values = 9.6 µg/l $\quad \frac{9.6}{6.7} = 1.4$ µg/l

Lowest chronic value = 6.8 µg/l

Table 4. Freshwater invertebrate chronic values for cyanide

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Reference
Isopod, *Asellus communis*	LC	29-40	34.1	Oseid & Smith, In press
Scud, *Gammarus pseudolimnaeus*	LC	16-21	18.3	Oseid & Smith, In press

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 25 µg/l $\frac{25}{5.1}$ = 4.9 µg/l

Lowest chronic value = 18.3 µg/l

Table 5. Freshwater plant effects for cyanide

Organism	Effect	Concentration (ug/l)	Reference
Blue-green alga, *Microcystis aeruginosa*	90% kill	7,790	Fitzgerald, et al. 1952

Lowest plant value = 7,790 ug/l

Table 6. Other freshwater data for cyanide

Organism	Test Duration	Effect	Result (ug/l)	Reference
Scud, Gammarus pseudolImnaeus	98 days	Competition with Asellus affects HCN toxicity	9	Oseid & Smith, In press
Cladoceran, Daphnia magna	96 hrs	LC50	160	Dowden & Bennett, 1965
Coho salmon, Oncorhynchus kisutch	2 hrs	Swimming speed reduced	10	Broderius, 1970
Chinook salmon (juvenile), Oncorhynchus tshawytscha	64 days	27% reduction in biomass	20	Negilski, 1973
Atlantic salmon, Salmo salar	58 days	Teratogenic effects to embryos	10	Leduc, 1978
Brook trout (fry), Salvelinus fontinalis	15.2 min	Death	8,640	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	10.8 min	Death	4,290	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	11.7 min	Death	2,130	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	26 min	Death	853	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	58 min	Death	392	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	210 min	Death	217	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	130 hrs	Death	50	Karsten, 1934
Brook trout (fry), Salvelinus fontinalis	27 days	100% survival	20	Karsten, 1934
Brook trout (juvenile), Salvelinus fontinalis	3.6 days	Lethal	80	Neil, 1957

Table 6. (continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Brook trout (juvenile) Salvelinus fontinalis	40 days	Not lethal	50	Neil, 1957
Brook trout (juvenile), Salvelinus fontinalis	25.5 min	75% reduction in swimming endurance	10	Neil, 1957
Rainbow trout (juvenile), Salmo gairdneri	250 min	Approximate median survival time	200	Dep. Sci. Ind. Res., 1956
Rainbow trout (juvenile), Salmo gairdneri	20 days	Abnormal oocyte development	10	Lesniak, 1977
Rainbow trout (adult), Salmo gairdneri	2 min	Mean survival time	2,000	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	8 min	Mean survival time	300	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	12 min	Mean survival time	250	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	12 min	Mean survival time	200	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	24 min	Mean survival time	180	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	72 min	Mean survival time	160	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	90 min	Mean survival time	140	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	2,525 min	Mean survival time	100	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	1,617 min	Mean survival time	90	Herbert & Merkens, 1952
Rainbow trout (adult), Salmo gairdneri	3,600 min	Mean survival time	80	Herbert & Merkens, 1952

Table 6. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Rainbow trout (adult), Salmo gairdneri	4,441 min	Mean survival time	70	Herbert & Merkens, 1952
Rainbow trout (juvenile), Salmo gairdneri	9 days	Weight gain reduced	10	Dixon, 1975
Rainbow trout (juvenile), Salmo gairdneri	4 days	Increased respiration rate	10	Dixon, 1975
Rainbow trout (juvenile), Salmo gairdneri	9 days	Liver damage (necrobiosis)	10	Dixon, 1975
Rainbow trout (yearling), Salmo gairdneri	21 days	65% reduction in weight gain	20	Speyer, 1975
Rainbow trout (yearling), Salmo gairdneri	21 days	75% reduction in swimming ability	20	Speyer, 1975
Rainbow trout, Salmo gairdneri	18 days	Production of spermatogonia reduced to 87%	10	Ruby & Dixon, Manuscript
Rainbow trout, Salmo gairdneri	18 days	Production of spermatogonia reduced to 51%	30	Ruby & Dixon, Manuscript
Brown trout (juvenile), Salmo trutta	6.58 min	Geometric mean time to death	1,006	Burdick, et al. 1958
Brown trout (juvenile), Salmo trutta	15 min	Geometric mean time to death	510	Burdick, et al. 1958
Brown trout (juvenile), Salmo trutta	30.1 min	Geometric mean time to death	320	Burdick, et al. 1958
Brown trout (juvenile) Salmo trutta	5 hrs	Oxygen uptake inhibited	25	Carter, 1962

1.2

Table 6. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Brown trout (fry), Salmo trutta	8.2 min	Death	8,030	Karsten, 1934
Brown trout (fry), Salmo trutta	8.9 min	Death	4,140	Karsten, 1934
Brown trout (fry), Salmo trutta	8.2 min	Death	2,070	Karsten, 1934
Brown trout (fry), Salmo trutta	140 min	Death	217	Karsten, 1934
Fathead minnow (juvenile), Pimephales promelas	5 days	LC50	120	Cardwell, et al. 1976
Channel catfish (juvenile), Ictalurus punctatus	26 hrs	LC50	161	Cardwell, et al. 1976
Guppy (juvenile), Lebistes reticulatus	120 hrs	Threshold concentration	236	Chen, 1968
Stickleback, Gasterosteus aculeatus	90 min	Depressed respiration rate	1,040	Jones, 1947
Threespine stickleback (adult), Gasterosteus aculeatus	824 min	Median survival time	134	Broderius, 1973
Threespine stickleback (adult), Gasterosteus aculeatus	642 min	Median survival time	170	Broderius, 1973
Threespine stickleback (adult), Gasterosteus aculeatus	412 min	Median survival time	237	Broderius, 1973
Bluegill (adult), Lepomis macrochirus	289 days	Survival reduced	67.8	Kimball, et al. 1978
Bluegill (adult), Lepomis macrochirus	289 days	No reproduction	5.4	Kimball, et al. 1978
Bluegill (juvenile), Lepomis macrochirus	202 min	Median survival time	198	Broderius, 1973

Table 6. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Bluegill (juvenile), Lepomis macrochirus	260 min	Median survival time	194	Broderius, 1973
Bluegill (juvenile), Lepomis macrochirus	351 min	Median survival time	165	Broderius, 1973
Bluegill (juvenile), Lepomis macrochirus	258 min	Median survival time	165	Broderius, 1973
Bluegill (juvenile), Lepomis macrochirus	352 min	Median survival time	144	Broderius, 1973
Bluegill (juvenile), Lepomis macrochirus	655 min	Median survival time	127	Broderius, 1973
Smallmouth bass (juvenile), Micropterus dolomieui	7.8 min	Geometric mean time to death	1,980	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	12.4 min	Geometric mean time to death	1,430	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	15.4 min	Geometric mean time to death	978	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	30.6 min	Geometric mean time to death	755	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	42.8 min	Geometric mean time to death	478	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	80.5 min	Geometric mean time to death	338	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	133 min	Geometric mean time to death	243	Burdick, et al. 1958
Smallmouth bass (juvenile), Micropterus dolomieui	290 min	Geometric mean time to death	175	Burdick, et al. 1958

Table 6. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Largemouth bass (juvenile), Micropterus salmoides	2 days	Significant increases in opercular rate	40	Morgan & Kühn, 1974

SALTWATER ORGANISMS

Introduction

The data base for the effects of cyanide on saltwater organisms is limited to a few studies on algae and an oyster.

Plant Effects

Two saltwater algal species (Webster and Hackett, 1965; Nelson and Tolbert, 1970) have been exposed to cyanide and there was an inhibition of respiration in Prototheca zopfi at 3,000 µg/l and enzyme inhibition in Chlorella sp. at 30,000 µg/l (Table 7). The Final Plant Value is 3,000 µg/l.

Miscellaneous

A short exposure of an oyster to cyanide (Usuki, 1956) resulted in the observation of a suppression in activity after 10 minutes of exposure to 150 µg/l (Table 8). After 3 hours there was an inhibition in activity at 30,000 µg/l.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

All values are for free cyanide expressed as CN. The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = not available

Final Acute Value = not available

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 3,000 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 3,000 µg/l

0.44 x Final Acute Value = not available

No saltwater criterion can be derived for free cyanide using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitue for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 7. Marine plant effects for cyanide

Organism	Effect	Concentration (ug/l)	Reference
Green alga, *Prototheca zopfi*	Respiration inhibition	3,000	Webster & Hackett, 1965
Green alga, *Chlorella* sp	Enzyme inhibition	30,000	Nelson & Tolbert, 1970

Lowest Plant value = 3,000 µg/l

Table 8. Other marine data for cyanide (Usuki, 1956)

Organism	Test Duration	Effect	Result (ug/l)
Oyster, *Crassostrea* sp.	10 mins	Activity suppression	150
Oyster, *Crassostrea* sp.	3 hrs	Activity inhibition	30,000

REFERENCES

Anderson, P., and L. Weber. 1975. Toxic response as a quantitative function of body size. Toxicol. Appl. Pharmacol. 33: 471.

Black, H.H., et al. 1957. Industrial waste guide--by-product coke. Proc. 11th Ind. Waste Conf. Purdue Univ. 41: 494.

Broderius, S.J. 1970. Determination of molecular hydrocyanic acid in water and studies of the chemistry and toxicity to fish of the nickelocyanide complex. M.S. thesis. Oregon State University, Corvallis.

Broderius, S.J. 1973. Determination of molecular hydrocyanic acid in water and studies of the chemistry and toxicity to fish of metal-cyanide complexes. Ph.D. thesis. Oregon State University, Corvallis.

Broderius, S., et al. 1977. Relative toxicity of free cyanide and dissolved sulfide forms to the fathead minnow, Pimephales promelas. Jour. Fish. Res. Board Can. 34: 2323.

Brown, V.M. 1968. The calculation of the acute toxicity of mixtures of poisons to rainbow trout. Water Res. 2: 723.

Burdick, G.E., et al. 1958. Toxicity of cyanide to brown trout and smallmouth bass. N.Y. Fish Game Jour. 5: 133.

Cairns, J. Jr., and A. Scheier. 1958. The effect of periodic low oxygen upon toxicity of various chemicals to aquatic organisms. Proc. 12th Ind. Waste Conf. Purdue Univ. Eng. Ext. Ser. No. 94, Eng. Bull. 42: 165.

Cairns, J. Jr., and A. Scheier. 1963. Environmental effects upon cyanide toxicity to fish. Notulae Naturae, Acad. Natural Sci., Philadelphia, No. 361.

Cairns, J. Jr., et al. 1965. A comparison of the sensitivity to certain chemicals of adult zebra danios Brachydanio rerio (Hamilton-Buchanan) and zebra danio eggs with that of adult bluegill sunfish Lepomis macrochirus Raf. Notulae Naturae, Acad. Natural Sci., Philadelphia, No. 381.

Cairns, J., Jr., et al. 1976. Invertebrate response to thermal shock following exposure to acutely sub-lethal concentrations of chemicals. Arch. Hydrobiol. 77: 164.

Cardwell, R., et al. 1976. Acute toxicity of selected toxicants to six species of fish. EPA 600/3-76-008. U.S. Environ. Prot. Agency

Carter, L. 1962. Bioassay of trade wastes. Nature 196: 1304.

Chen, C.W. 1968. A kinetic model of fish toxicity threshold. Ph.D. thesis. University of California, Berkeley.

Department of Scientific and Industrial Research. 1956. Water pollution research 1955. H.M. Stationery Off. London.

Dixon, D.G. 1975. Some effects of chronic cyanide poisoning on the growth, respiration and liver tissue of rainbow trout. M.S. thesis. Concordia University, Montreal.

Doudoroff, P. 1956. Some experiments on the toxicity of complex cyanides to fish. Sewage Ind. Wastes 28: 1020.

Doudoroff, P., et al. 1966. Acute toxicity to fish of solutions containing complex metal cyanides, in relation to concentrations of molecular hydrocyanic acid. Trans. Am. Fish. Soc. 95: 6.

Dowden, B.F., and H.J. Bennett. 1965. Toxicity of selected chemicals to certain animals. Jour. Water Pollut. Control Fed. 37: 1308.

Fitzgerald, G.P., et al. 1952. Studies on chemicals with selective toxicity to blue-green algae. Sewage Ind. Wastes 24: 888.

Henderson, C., et al. 1961. The effects of some organic cyanides (nitriles) on fish. Proc. 15th Ind. Waste Conf. Purdue Univ. Eng. Ext. Ser. No. 106. Eng. Bull. 45: 120.

Herbert, D.W.M., and J.C. Merkens. 1952. The toxicity of potassium cyanide to trout. Jour. Exp. Biol. 29: 632.

Izatt, R.M., et al. 1962. Thermodynamics of metal-cyanide coordination. I. pK, H^{o}, and S^{o} values as a function of temperature for hydrocyanic acid dissociation in aqueous solution. Inorg. Chem. 1: 828.

Jones, J.R.E. 1947. The oxygen consumption of Gasterosteus aculeatus L. in toxic solutions. Jour. Exp. Biol. 23: 298.

Karsten, A. 1934. Investigations of the effect of cyanide on Black Hills trout. Black Hills Eng. 22: 145.

Kimball, G., et al. 1978. Chronic toxicity of hydrogen cyanide to bluegills. Trans. Am. Fish. Soc. 107: 341.

Koenst, W., et al. 1977. Effect of chronic exposure of brook trout to sublethal concentrations of hydrogen cyanide. Environ. Sci. Technol. 11: 883.

Leduc, G. 1978. Deleterious effects of cyanide on early life stages of Atlantic salmon (Salmo salar). Jour. Fish. Res. Board Can. 35: 166.

Lee, D. 1976. Development of an invertebrate bioassay to screen petroleum refinery effluents discharged into freshwater. Ph.D. thesis. Virginia Polytechnic Inst. State University, Blacksburg.

Lesniak, J.A. 1977. A histological approach to the study of sublethal cyanide effects on rainbow trout ovaries. M.S. thesis. Concordia University, Montreal.

Lind, D., et al. 1977. Chronic effects of hydrogen cyanide on the fathead minnow. Jour. Water Pollut. Control Fed. 49: 262.

Lipschuetz, M., and A.L. Cooper. 1955. Comparative toxicities of potassium cyanide and potassium cuprocyanide to the western blacknosed dace (Rhinichtys atratulus meleagris). N.Y. Fish Game Jour. 2: 194.

Morgan, W.S.G., and P.C. Kuhn. 1974. A method to monitor the effects of toxicants upon breathing rates of largemouth bass (Micropterus salmoides Lacepede). Water Res. 8: 67.

Negilski, D.S. 1973. Individual and combined effects of cyanide pentachlorphenol and zinc on juvenile chinook salmon and invertebrates in model stream communities. M.S. thesis. Oregon State University, Corvallis.

Neil, J.H. 1957. Some effects of potassium cyanide on speckled trout (Salvelinus fontinalis). Pages 74-96 in Papers presented at 4th Ontario Ind. Waste Conf. Water Pollut. Adv. Comm., Ontario Water Resour. Comm., Toronto.

Nelson, E.B., and N.E. Tolbert. 1970. Glycolate dihydrogenase in green algae. Arch. Biochem. Biophys. 141: 102.

Oseid, D., and L. Smith. The effects of hydrogen cyanide on Asellus communis and Gammarus pseudolimnaeus and changes in their competitive response when exposed simultaneously. Bull. Environ. Contam. Toxicol. (In press).

Patrick, R., et al. 1968. The relative sensitivity of diatoms, snails, and fish to twenty common constituents of industrial wastes. Prog. Fish-Cult. 30: 137.

Roback, S.S. 1965. Environmental requirements of Trichoptera. Pages 118-126 in Biological problems in water pollution. 3rd Seminar (1962), R.A. Taft Sanit. Eng. Center, Cincinnati, Ohio.

Ruby, S.M., and D.G. Dixon. Influence of sublethal concentrations of cyanide on early stages of spermatogenesis in rainbow trout, Salmo gairdneri. Water Pollut. Res Lab., Concordia University, Montreal. (Manuscript.)

Smith, L., et al. 1978. Acute toxicity of hydrogen cyanide to freshwater fishes. Arch. Environ. Contam. Toxicol. 7: 325.

Smith, L.L. Jr., et al. 1979. Acute and chronic toxicity of HCN to fish and invertebrates. Ecol. Rep. Ser. EPA-600/3-79-009. U.S. Environ. Prot. Agency.

Speyer, M.R. 1975. Some effects of chronic combined arsenic and cyanide poisoning on the physiology of rainbow trout. M.S. thesis. Concordia University, Montreal.

Turnbull, H., et al. 1954. Toxicity of various refinery materials to fresh-water fish. Ind. Eng. Chem. 46: 324.

Usuki, I. 1965. A comparison of the effects of cyanide and azide on the ciliary activity of the oyster gill. Sci. Rep. Tohoku University, Fourth Sci. 22: 137.

Wallen, I.E., et al. 1957. Toxicity to Gambusia affinis of certain pure chemicals in turbid waters. Sewage Ind. Wastes 29: 695.

Webster, D.A., and D.P. Hackett. 1965. Respiratory chain of colorless algae. I. Chlorophyta and Euglenophyta. Plant Physiol. Lancaster. 40: 1091.

CYANIDES

Mammalian Toxicology and Human Health Effects

Summary

Cyanides are defined as hydrogen cyanide (HCN) and its salts. The toxicological effects of cyanides are based upon their potential for rapid conversion by mammals to HCN. Various organic compounds containing the CN moiety which may have a potential for conversion to HCN *in vivo* will not be considered in this document. Cyanides have long been feared for their high lethality and their fulminating action. At the present time, however, cyanides do not constitute an important or widespread environmental health problem. Almost all examples of human cyanide poisoning or adverse environmental effects in the past have involved occupational exposures or relatively localized sources of pollution. Cyanides are uncommon in U.S. water supplies and in the atmosphere. Although some food plants clearly can cause acute cyanide poisoning if ingested in sufficient amount, the evidence associating cyanide compounds in other plants with chronic neuropathies is not convincing.

Some evidence suggests that the uses of cyanide in the U.S. are increasing, and, therefore, continued vigilance in the form of monitoring is indicated. However a number of properties and characteristics of cyanide indicate that it will probably remain only a potential pollutant or one of secondary concern. For example, cyanide has a low degree of persistence in the environment and it is not accumulated or stored in any mammalian species that has been studied.

In keeping with the latter, a sizeable body of experimental evidence suggests that cyanide has an unusually low degree of chronic toxicity. It does not appear to be mutagenic, teratogenic, or carcinogenic.

No new evidence was encountered to suggest that the P.H.S. drinking water standard for cyanide set in 1962 should be lowered (Natl. Inst. Occup. Safety Health, 1969).

EXPOSURE

Introduction

Cyanides are defined as hydrogen cyanide (HCN) and its salts. The toxicological effects of cyanides are based upon their potential for rapid conversion by mammals to HCN.

Cyanide production in the U.S. is now over 700 million pounds per year and it appears to be increasing steadily (Towill, et al. 1978). The sources and industrial uses of cyanide compounds in the United States have recently been reviewed exhaustively (Natl. Inst. Occup. Safety Health 1976; Towill, et al. 1978). Briefly, the major industrial users of cyanide in the U.S. are the producers of steel, plastics, synthetic fibers and chemicals, and the electroplating and metallurgical industries. In addition to these industries (see Table 1) cyanide wastes are discharged into the environment from the pyrolysis of a number of synthetic and natural materials and from chemical, biological, and clinical laboratories. Although wool, silk, polyacrylonitrile, nylon, polyurethane, and paper are all said to liberate HCN on combustion, the amounts vary widely with the conditions. As yet there is no standardized fire toxicity test protocol in the U.S. (Terrill, et al. 1978).

Despite numerous potential sources of pollution, cyanide is relatively uncommon in most U.S. water supplies. A survey of 969 U.S. public water supply systems in 1970 revealed no cyanide concentrations above the mandatory limit (McCabe, et al. 1970). In 2,595 water samples, the highest cyanide

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TABLE 1 INORGANIC CYANIDE WASTES

Source and Material	Bureau of the Census regions									Total
	I	II	III	IV	V	VI	VII	VIII	IX	
Annual waste production (lb/year)										
Cyanides from electroplating	2.78×10^6	6.07×10^6	6.86×10^6	0.96×10^6	1.04×10^6	0.49×10^6	0.77×10^6	0.15×10^6	2.20×10^6	21.32×10^6
Paint sludge										
cyanides	1,000	9,900	13,800	2,900	3,850	2,150	3,350	550	7,300	44,900
sludge	0.92×10^6	8.12×10^6	11.32×10^6	2.40×10^6	3.16×10^6	1.76×10^6	2.74×10^6	0.44×10^6	5.97×10^6	36.83×10^6
Paint residue										
cyanides	0.18×10^5	0.57×10^5	0.62×10^5	0.23×10^5	0.47×10^5	0.20×10^5	0.30×10^5	0.13×10^5	0.41×10^5	3.11×10^5
old paint	13×10^6	41×10^6	44×10^6	16×10^6	34×10^6	14×10^6	21×10^6	9×10^6	29×10^6	221×10^6
Stored wastes (lb)										
Sodium cyanide		1,400						16		1,416
Calcium cyanide							180		25	205
Copper cyanide		100						32		132
Potassium cyanide					2					2
Silver cyanide								16	10	26
Potassium ferricyanide					4					4
Potassium ferrocyanide						12				12

Source: Ottinger, et al. 1973, Table 1.

concentration found was 8 ppb and the average concentration was 0.09 ppb (Towill, et al. 1978). In part, this must be ascribed to the volatility of undissociated hydrogen cyanide which would be the predominant form in all but highly alkaline waters. Also, in part, cyanide ion would have a decided tendency to be "fixed" in the form of insoluble or undissociable complexes by trace metals. In view of the increased production and uses of cyanide in the U.S., however, continued vigilance in the form of monitoring is certainly indicated particularly in the proximity of known potential sources of pollution. Techniques for monitoring have been reviewed elsewhere (Natl. Inst. Occup. Safety Health, 1976; Towill, et al. 1978).

Ingestion from Water

As noted above, cyanide is an uncommon pollutant in most U.S. water supplies and documented examples of levels in excess of the 1962 P.H.S. limits (U.S. Pub. Health Serv. 1962) are extremely rare. No human cases of illness or death due to cyanide in water supplies are known. The lack of such documentation, of course, cannot be accepted complacently. It is entirely possible that pulse discharges of industrial wastes result in high localized concentrations which have escaped detection, but general recognition of the high toxicity of cyanide has made its removal standard practice in most industries (Reed, et al. 1971). Fortunately, known methods for cyanide removal including alkaline chlorination, hypochlorite treatment, reaction with aldehydes, electrolytic decomposition, exposure to ionizing radiation, and heating are effective and relatively economical (Lawes, 1972; Watson,1973).

A few accidents have resulted in massive fish kills, some livestock deaths, and environmental damage. Cyanide, unknowingly released from a sewage plant in Oak Ridge, Tenn., was responsible for the death of 4,800 fish in Melton Hill Lake near the sewage outfall (The Oak Ridge, 1975). About 1,500 55- and 30-gallon drums containing cyanides disposed of near Byron, Ill. resulted in long-range environmental damage and livestock death. Surface water runoff from the area contained up to 365 ppm cyanide (Towill, et al. 1978).

Ingestion from Foods

Except for certain naturally occurring organonitriles in plants, it is uncommon to find cyanide in foods in the

U.S. In higher plants the major group of organonitriles are the cyanogenic glycosides and at least 20 distinct compounds are known. Perhaps the best known of this group is the compound, amygdalin, which is found in many parts of the cherry laurel and the seeds of cherries, plums, peaches, apricots, apples, and pears. Amygdalin is the chief ingredient in Laetrile. Both Laetrile and amygdalin-containing fruit pits have been implicated as causes of acute cyanide poisoning in humans (Braico, et al. 1979; Gosselin, et al. 1976). The release of free cyanide from cyanogenic glycosides can be effected by acid hydrolysis or most rapidly by β-glucosidases, enzymes present in plants and in the intestinal microflora of mammals but found in only trace amounts in animal tissues (Conchie, et al. 1959).

Another naturally occurring group of organonitriles are called the pseudocyanogenic glycosides of which the best known example is cycasin from the Cycadaceae species. As implied by the name, cyanide release from these compounds is unlikely to occur in vivo since alkaline hydrolysis is required (Miller, 1973). Cycasin and related glycosides are highly toxic and their ingestion along with foodstuffs has been implicated in a variety of so-called "tropical neuropathies" and amblyopias (Osuntokun, 1968). Although these neurological disturbances have frequently been cited in the literature (Towill, et al. 1978) as examples of "chronic cyanide poisoning," the evidence for that extrapolation is indirect and inconclusive. The failure of repeated attempts to produce similar syndromes with pure hydrogen cyanide or its salts (below), strongly suggests that the neuropathies

produced by cycasin-containing foods are due to other unrecognized toxins, to the cycasin per se, or to uncharacterized toxic metabolites rather than to cyanide.

Other organonitriles found in plants include the lathyrogenic compounds, such as α-glutamyl-β-cyanoalanine, the glucosinolates such as glucobrassicin, and the cyanopyridine alkaloids such as ricinine and indoleacetonitrile (Towill, et al. 1978). Although many of these are toxic to mammals, no evidence links their toxicity to cyanide poisoning.

Inhalation

Hydrogen cyanide vapor is absorbed rapidly through the lungs (Gettler and St. George, 1934). Because HCN has a pKa of 9.2 and exists primarily as the acid under biological conditions, absorption across the alveolar membrane should be rapid (Wolfsie and Shaffer, 1959). Human inhalation of 270 ppm HCN vapor brings death immediately, while 135 ppm is fatal after 30 minutes (Dudley, et al. 1942).

Cyanide absorption following inhalation of very low concentrations is indicated by the observation that smokers have higher thiocyanate levels in plasma and other biological fluids than do nonsmokers (Wilson and Matthews, 1966). Cyanide levels usually are not significantly different in smokers as compared with non-smokers (Pettigrew and Fell, 1973; Wilson and Matthews, 1966), since cyanide absorbed from inhaled tobacco smoke is rapidly converted to thiocyanate (Johnstone and Plimmer, 1959; Pettigrew and Fell, 1973). Inhalation of cyanide salt dusts is also dangerous because the cyanide will dissolve on contact with moist mucous membranes and be absorbed into the bloodstream (Davison, 1969;

Knowles and Bain, 1968).

The so-called distinctive odor of bitter almonds ascribed to HCN does not necessarily serve as a warning of exposure. The ability to smell hydrogen cyanide appears to be a genetically determined trait. Individuals vary widely from not being able to detect the odor at all to extreme sensitivity (Kirk and Stenhouse, 1953).

Dermal

Hydrogen cyanide in either liquid or vapor form is absorbed through the skin (Drinker, 1932; Potter, 1950; Tovo, 1955; Walton and Witherspoon, 1926). Absorption is probably increased if the skin is cut, abraded, or moist. Many accidents involving skin contamination also involve inhalation exposure; the contribution due to skin absorption in these cases is difficult to assess. Potter (1950) described a case in which liquid HCN ran over the bare hand of a worker wearing a fresh air respirator. Cyanide inhalation was prevented, but the worker collapsed into deep unconsciousness within five minutes, suggesting significant percutaneous absorption.

PHARMACOKINETICS

Absorption

Probably the common inorganic cyanides of commerce are rapidly absorbed from the stomach and duodenum. Certainly, the human experience in regard to the rapidly lethal effects (Gosselin, et al. 1976) of ingested cyanides is in accord with the above, but experimental studies which actually define quantitatively the rates of penetration are not available.

Hydrogen cyanide is a weak acid with a pK_a of 9.2. Thus, the acid milieu of the stomach would greatly favor the undissociated species, HCN, which should further hasten absorption. Even at the physiological pH of 7.4, however, cyanide would exist predominantly as the unionized moiety which would serve to facilitate its transfer among various body compartments (see above). In accord with the theory of non-ionic diffusion cyanide would be predicted to accumulate in body compartments which are at a higher pH (more alkaline) than blood. At present, no evidence can be cited to substantiate directly that prediction.

It has long been common knowledge that hydrogen cyanide gas or vapors are rapidly absorbed via the lungs producing reactions within a few seconds and death within minutes (Gosselin, et al. 1976). Hydrogen cyanide was used as the instrument of execution for convicted criminals in some U.S. States primarily because of its rapid lethal effects on inhalation of high concentrations.

Hydrogen cyanide gas or solutions are absorbed through the intact skin much more readily than are the ionized salts which are less lipid soluble (Wolfsie and Shaffer, 1959). Absorption is probably increased in both cases if the skin has been cut or abraded. Alleged cases of human skin absorptions, however, are often complicated by the possibility of concomitant inhalation of cyanide gas (see also Dermal, above). Again, quantitative estimates of the rate of penetration of skin by various forms of cyanide are not available.

Distribution

Cyanide is distributed to all organs and tissues via the blood where its concentration in red cells is greater than that in plasma by a factor of two to three. Presumably, the accumulation of cyanide in erythrocytes is a reflection of its binding to methemoglobin which is found normally in the blood of non-smokers in concentrations amounting to as much as two percent of the total circulating pigment (Smith and Olson, 1973). However, there may be other factors as yet unrecognized which favor the accumulation of cyanide in red cells. Cyanide may also accumulate locally in body cells because of binding to metalloproteins or enzymes such as catalase or cytochrome c oxidase (Smith, et al. 1977). The possibility of concentration differences due to pH gradients between body compartments was mentioned above. Certainly, one would predict that cyanide would readily cross the placenta, but again quantitative data are lacking.

Metabolism

By far, the major pathway for the metabolic detoxication of cyanide involves its conversion to thiocyanate via the enzyme rhodanese (de Duve, et al. 1955). Rhodanese is widely distributed in the body, but the highest activity is found in mammalian liver (Table 2). The rate of the rhodanese reaction *in vivo* is limited by the availability of the endogenous sulfur containing substrate, the identity of which is still unknown. Thiosulfate can serve as a substrate for rhodanese with a high degree of efficiency both *in vivo* and *in vitro* (Chen and Rose, 1952; Himwich and Saunders, 1948).

TABLE 2

RHODANESE ACTIVITY IN TISSUES OF THE DOG, RHESUS MONKEY, RABBIT, AND RAT
(mg CN converted to CNS per gram of tissue)

Tissue	Dog		Rhesus Monkey		Rabbit		Rat	
	Range[a]	Number of observations	Range[a]	Number of observations	Range	Number of observations	Range	Number of observations
Suprarenals								
whole	2.14-3.60 (5.46, 4.50)	6	0.14-1.35	3	1.24-3.94	2	0.27-0.41	2
cortex	2.86-5.62	2						
medulla	0.27-1.12	2						
Liver	0.78-1.46 (4.91, 6.28)	7	10.98-15.16 (5.98)	4	7.98-18.92	9	14.24-28.38	9
Brain								
cortex	0.34-0.92	7	0.27	1	1.41-1.44	2	0.70-0.72	2
caudate nucleus	0.27-1.06	7	0.34-0.50	2	0.13-0.18	2		
midbrain	0.52-1.35	6	0.22-0.80	2	1.17-1.39	2	0.73-1.13	2
cerebellum	0.21-1.22	7	0.33	1	0.63-1.24	2		
medulla	0.38-1.52	7	0.49-0.85	2	0.91	1		
Spinal cord								
cervical	0.15-1.08	7	0.56-0.57	2	0.89-0.90	2	0.16-0.18	2
lumbar	0.12-0.84	4	0.20-0.42	2	0.35-1.74	2	0.23-0.27	2
sacral	0.16-1.41	4	0.23-0.28	2	0.59-1.10	3	0.56-0.74	2
Heart	0.11-0.14	6	0.48-0.82	3				
Kidney	0.42-0.74	6	2.46-3.58	4	6.20-7.69	3	10.44-11.08	2
Testes	0.32-0.41	5	0.38-0.46	3	0.32-0.36	2	1.24-1.61	2
Epididymis	0.29	1						
Ovaries	0.42	1			0.30	1		
Lung	0.16-0.17	3	0.11-0.21	2	0.40	1		
Spleen	0.10-0.14	2	0.12-0.34	2	0.20	1		
Muscle	0.03-0.19	6	0.23-0.57	3	0.18	1		
Intestine								
duodenum	0.05-0.11	3						
jejunum	0.04	1						
Eye	0.02	1						
Optic nerve	0.35	1						

TABLE 2 (Cont.)

Tissue	Dog		Rhesus Monkey		Rabbit		Rat	
	Range[a]	Number of observations	Range[a]	Number of observations	Range	Number of observations	Range	Number of observations
Salivary gland, parotid	0.05-0.36	3	0.99	1				
Lymph node	0.08-0.13	2						
Pancreas	0.14-0.28	4	0.12-0.44	2				
Thyroid	0.05-0.94	3						
Anterior pituitary	0.26	1						
Whole blood	0.01-0.02	2						
Erythrocytes	0.01-0.02	2						
Plasma	0.01	1						

[a]Figures in parentheses are single observations falling outside the normal range.

Source: Adapted from Himwich and Saunders, 1948, Table 1, p. 351. Reprinted by permission of the publisher.

Alternative minor metabolic pathways for cyanide metabolism include conjugation with cysteine to form 2-iminothiazolidene-4-carboxylic acid, a reaction that is said to proceed nonenzymatically (Figure 1). In rats given a total dose of 30 mg over an eight-day period, this pathway accounts for no more than 15 percent of the total cyanide (Wood and Cooley, 1956). A very small fraction of the total cyanide is bound by hydroxocobalamin, probably less than 1 percent (Brink, et al. 1950). A small amount (about one to two percent) is excreted unchanged as HCN via the lungs (Friedberg and Schwarzkopf, 1969). By reactions that are not well understood, cyanide gains access to metabolic pathways for one carbon compounds and it is converted to formate and to carbon dioxide.

Excretion

As estimated in rats given 30 mg sodium cyanide intraperitoneally over a period of eight days, 80 percent of the total cyanide is excreted in the urine in the form of thiocyanate (Wood and Cooley, 1956). Because the fate of cyanide is largely determined by a single metabolic pathway, one would predict that it would fit a relatively simple pharmacokinetic model, e.g., first order kinetics in plasma, but such detailed analyses have not been made. Cyanide does not appear to accumulate significantly in any body compartment with repeated doses or chronic exposures.

Because the liver contains the highest activity of rhodanese, it is possible that pre-existing liver disease might slow the rate of cyanide metabolism, but no studies appear to address this question. No inhibitors of rhodanese are known which are active *in vivo*.

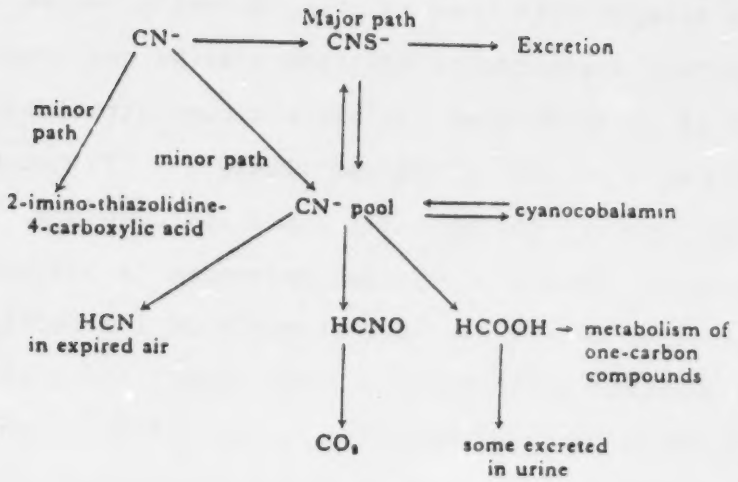

Figure 1. Fate of cyanide ion in the body. Source: Williams, 1959, p. 393. Reprinted by permission of the publisher.

EFFECTS

Acute, Sub-acute and Chronic Toxicity

Hydrogen cyanide and its alkali metal salts are chemicals of high inherent lethality to man and other mammals. The mean lethal dose of these substances by mouth in human adults is in the range of 50 to 200 mg (1 to 3 mg/kg), and death is rarely delayed more than an hour (Gosselin, et al. 1976). In respiratory exposures to hydrogen cyanide gas, death occurs in 10 to 60 minutes at ambient concentrations of 0.1 to 0.3 mg/l or 100 to 300 ppm (Table 3). In non-fatal poisonings recovery is generally rapid and complete.

The acute effects of cyanide poisoning in all obligate aerobic species can be ascribed directly or indirectly to a single specific biochemical lesion, namely the inhibition of cytochrome c oxidase (Gosselin, et al. 1976). Inhibition of this terminal enzyme complex in the respiratory electron transport chain of mitochondria impairs both oxidative metabolism and the associated process of oxidative phosphorylation (Lehninger, 1975). The ensuing syndrome has been well characterized in man and in laboratory animals (e.g., Gosselin, et al. 1976). In its major features cyanide poisoning resembles the effects of acute hypoxia whether the latter is due to airway obstruction or to the absence of oxygen (anoxic hypoxia), carbon monoxide poisoning (anemic hypoxia) or shock (stagnant or hypokinetic hypoxia), all of which result in a decreased supply of oxygen to peripheral tissues.

Cyanide poisoning differs from other types of hypoxia in that the oxygen tension in peripheral tissues usually remains normal or may even be elevated (Brobeck, 1973).

TABLE 3

HUMAN RESPONSE TO INHALED CYANIDE AND CYANIDE-CONTAINING COMPOUNDS

Compound	Cyanide concentration (mg/liter)	Cyanide concentration (ppm)	Response	Reference
Hydrogen cyanide	0.3	270	Immediately fatal	Prentiss, 1937
	0.2	181	Fatal after 10-min exposure	Prentiss, 1937
	0.15	135	Fatal after 30-min exposure	Prentiss, 1937
	0.12-0.15	110-135	Fatal after ½ to 1 hr or later, or dangerous to life	Fassett, 1963
Cyanogen		16	Nasal and eye irritation after 6 to 8 min	McNerney and Schrenk, 1960
Cyanogen chloride	0.40	159	Fatal after 10-min exposure	Prentiss, 1937
	0.120	48	Fatal after 30-min exposure	Fassett, 1963
	0.005	2	Intolerable concentration, 10-min exposure	Fassett, 1963
	0.0025	1	Lowest irritant concentration, 10-min exposure	Fassett, 1963
Cyanogen bromide	0.40	92	Fatal after 10-min exposure	Prentiss, 1937
	0.035	8	Intolerable concentration	Prentiss, 1937
	0.006	1.4	Greatly irritating to conjunctiva and the mucous membranes of the respiratory system	Prentiss, 1937

This paradoxical difference arises because the effect of cyanide is to block the utilization of oxygen by aerobic cells, a novel condition referred to as histotoxic hypoxia. The organ systems most profoundly affected, however, are the same as those impaired in any hypoxia irrespective of etiology, namely the brain and the heart because of their high dependence on oxidative metabolism. Two signs associated with cyanide poisoning in man (e.g., Gosselin, et al. 1976) follow from the preceding: 1) The failure to utilize molecular oxygen in peripheral tissues results in abnormally high concentrations of oxyhemoglobin in the venous return which accounts for a flush or brick-red color of the skin; and 2) attempts to compensate for the inhibition of oxidative metabolism leads to increased demands on glycolysis which accounts for a metabolic (lactic) acidosis.

A special but less unique effect of cyanide is stimulation of the chemoreceptors of the carotid body which elicits a characteristic pattern of reflex activity (Heymans and Neil, 1958). Since the nature of these chemoreceptors is unknown, it is possible that the effect of cyanide on them is due also in some way to the inhibition of cytochrome c oxidase. Stimulation of the carotid body chemoreceptors by cyanide results in an immediate, well-sustained, and marked augmentation of the respiration. Circulatory effects which often accompany the increase in ventilation include a transient rise in blood pressure which is probably secondary to a reflex sympathetic discharge. The rise in blood pressure is often accompanied by a bradycardia which some authorities insist is not due to the common baroreceptor reflex via

the vagus nerves. The pressor response is followed by a fall in blood pressure to hypotensive levels from which the victim may not recover (Heymans and Neil, 1958).

The other prominent effect of cyanide on the respiration is a direct depression or fatal arrest which is the result of an action of cyanide at the level of the brain stem nuclei responsible for the control of breathing. In poisoned victims, the heart beat invariably outlasts breathing movements. The cardiac irregularities often noted may be secondary to respiratory embarrassment, but direct histotoxic effects of cyanide on myocardial cells are an even more likely mechanism.

Massive doses by mouth or concentrated respiratory exposures may result in a sudden loss of consciousness which may simply represent fainting secondary to the late fall in blood pressure noted above. Presumably, the histotoxic hypoxia triggers a massive peripheral vasodilation resulting in orthostatic hypotension and collapse. The sequence of events is slower on exposure to lower concentrations (Table 3) and victims may experience anxiety, confusion, vertigo, and giddiness before loss of consciousness. Unconsciousness is followed by asphyxial convulsions which may be violent and generalized. Opisthotonus, trismus, and incontinence are common. The seizures may be followed by a brief period of paralysis or rigidity with death in apnea (Gosselin, et al. 1976).

Despite the high lethality of large single doses or acute respiratory exposures to high vapor concentrations of cyanide, repeated sublethal doses do not result in cumulative adverse effects. Thus, cyanide is an example of a

chemical which has a high acute toxicity, but an unusually low degree of subacute or chronic toxicity. Hertting, et al. (1960) gave once or twice each day to dogs doses (0.5 to 2 mg/kg) of sodium cyanide that usually resulted in acute toxic signs but from which the animals recovered completely within half an hour. This regimen was continued over a period of 15 months with no evident pathophysiologic changes in organ function or permanent alteration in intermediary metabolism. Similarly, rats tolerated the equivalent of an acute oral LD_{50} of potassium cyanide each day for 25 days when it was mixed with their regular diet (Hayes, 1967).

Workers at American Cyanamid (1959) fed to beagle dogs a diet containing 150 ppm sodium cyanide for 30 days without observing a significant effect on their food consumption, hematologic parameters, behavioral characteristics, or microscopic changes in their organs or tissues. Howard and Hanzal (1955) fed a diet that had been fumigated with cyanide gas and contained the equivalent of 100 to 300 ppm hydrogen cyanide to rats for two years also with essentially negative findings. The conclusion that cyanide in substantial but sublethal intermittent doses can be tolerated for long periods of time and perhaps indefinitely seems inescapable.

It seems reasonable to assume that continuous exposure to some as yet undefined but low concentration of hydrogen cyanide gas will lead inevitably to an exhaustion of the reserve capacity of mammals to inactivate and detoxify cyanide. The rate at which cyanide can be inactivated acutely has been measured in guinea pigs. By continuously infusing cyanide solutions intravenously at different rates Lendle

(1964) showed that at a rate of 0.076 mg kg^{-1} min^{-1} about 90 percent of the single lethal dose as determined by "bolus" injection could be detoxified over the course of an hour. When the rate of administration was slowed, multiple lethal doses could be tolerated. Extrapolation to a dose rate that could be tolerated indefinitely, however, does not seem justified with such a highly artificial model system.

Synergism and/or Antagonism

Since cyanide acts by inhibiting cytochrome c oxidase, it is reasonable to presume that any other established inhibitor of the same enzyme would have toxic effects synergistic with (or additive to) those of cyanide. An established example of such a substance is sulfide which is encountered as hydrogen sulfide gas or as the alkali metal salts (Smith and Gosselin, 1979). Sulfide is even more potent than is cyanide as an inhibitor of cytochrome c oxidase, and similarities between sulfide and cyanide inhibition suggest that they act by similar mechanisms (Nicholls, 1975; Smith, et al. 1977). No specific experimental studies can be cited, however, on the combined effects of cyanide and sulfide in either *in vitro* or *in vivo* systems.

The only other established inhibitor of cytochrome c oxidase is azide (given either as hydrazoic acid or its alkali metal salts). Azide is a much weaker inhibitor of cytochrome c oxidase than is cyanide or sulfide, and it appears to act by a different inhibitory mechanism (Smith, et al. 1977). Again, no specific studies can be cited to establish whether azide has synergistic or additive effects in combination with cyanide.

Although cyanide produces the cellular equivalent of hypoxia, there is no reason to suppose that other causes of hypoxia would have effects additive to or synergistic with those of cyanide. By coincidence one cause of anemic hypoxia (Brobeck, 1973), namely, methemoglobinemia, is a specific antagonist to cyanide (below). Oxygen has no effect on cyanide inhibition of cytochrome c oxidase *in vitro*, and it does not reverse the course of cyanide poisoning *in vivo*. Since cyanide blocks the utilization of molecular oxygen in peripheral tissues, its effects on oxygen tension are opposite in direction to those of "true" hypoxia. Since cytochrome c oxidase has a very high affinity for molecular oxygen, it seems unlikely that the oxygen tension in peripheral tissues in cyanide poisoning is ever a limiting parameter.

Cyanide poisoning is specifically antagonized by any chemical agent capable of rapidly generating methemoglobin *in vivo* such as sodium nitrite, hydroxylamine, amyl nitrite, and a large number of aromatic amino- and nitro-compounds such as aniline, p-aminopropiophenone and nitrobenzene (Smith and Olson, 1973). Methemoglobin binds cyanide tightly in the form of the biologically inactive complex, cyanmethemoglobin. From a therapeutic standpoint there are several disadvantages to the induction of methemoglobinemia despite its established efficacy. Cyanmethemoglobin is a dissociable complex and eventually the dissociation of free cyanide from it may result in a recurrence of symptoms. The procedure is limited by the concentration of methemoglobin that can be tolerated by the victim, and the chemicals used to generate

methemoglobin have toxic side effects of their own (Gosselin, et al. 1976).

A second therapeutically useful approach to the antagonism of cyanide poisoning is to provide an exogenous substrate for the enzyme rhodanese, which converts cyanide to the considerably less toxic form of thiocyanate. The endogeneous substrate for rhodanese is not known, but p-toluene thiosulfonate ($CH_3C_6H_4-SO_2-S^-$)is 4.5 times more active than thiosulfate as a substrate in vitro (Sorbo, 1953). Ethyl thiosulfate ($C_2H_5-S-SO_3-0^-$), ethyl xanthate ($C_2H_5OCS_2^-$), diethyl dithiocarbamate $(C_2H_5)_2NCS_2^-$), hydrosulfite ($S_2O_4^=$)and colloidal sulfur are all inactive as substrates for rhodanese (Sorbo, 1953). It is probable that other sulfur compounds as yet untested can also serve as substrates for rhodanese.

A variety of cobalt compounds effectively antagonize cyanide poisoning presumably by reacting chemically with free cyanide, e.g., cobaltous chloride, hydroxocobolamine, cobalt EDTA. The latter two compounds have been used in humans (Gosselin, et al. 1976). Although oxygen alone has no effect on cyanide poisoning, it is said to potentiate the anti-cyanide actions of thiosulfate and particularly the thiosulfate-nitrite combination (Way, et al. 1966).

Teratogenicity, Mutagenicity, Carcinogenicity

There are no data on teratogenic, mutagenic, or carcinogenic effects of cyanide nor do there appear to be any published studies with analagous compounds from which one might postulate the possible adverse effects of long-term, low-level exposure. As previously indicated, above a number of studies designed to show chronic or cumulative adverse effects yielded only

negative findings. It is possible that cyanide has antineoplastic activity; at least one study (Perry, 1935) reported a low therapeutic index for cyanide against rat sarcomas.

In contrast, thiocyanate, the major product of cyanide detoxification *in vivo* has produced developmental abnormalities in the chick (Nowinski and Pandra, 1946) and ascidian embryo (Ortolani, 1969) at high concentrations. Unfortunately, these studies with thiocyanate cannot be extrapolated to man nor can those of Hrizu, et al. (1973) who reported a cytostatic effect of thiocyanate on human KB cells in culture as well as an increased survival rate in mice inoculated with Ehrlich ascites tumor cells. Again, the amounts used preclude any meaningful extrapolation to human patients. Thus, there is no evidence that chronic exposure to cyanide results in teratogenic, mutagenic, or carcinogenic effects.

CRITERION FORMULATION

Existing Guidelines and Standards

The U.S. Public Health Service Drinking Water Standards of 1962 established 0.2 mg CN^-/l as the acceptability criterion for water supplies. In addition to defining the 0.2 mg/l criterion for cyanide the PHS set forth an "objective" to achieve concentrations below 0.01 mg CN^-/l in water "because proper treatment will reduce cyanide levels to 0.01 mg/l or less" (U.S. Pub. Health Serv. 1962). The Canadian government has recently adopted criterion and objective concentrations of 0.2 mg CN^-/l and 0.02 mg CN^-/l, respectively. The latter figure represents the lower limit of detection by colorimetric methods (Health Welfare Can. 1977).

The U.S. PHS criterion was based on cyanide toxicity to fish and not to man. Obviously, a disparity exists between the exposure condition for man and for fish. The human experience cited involved discrete single doses by mouth whereas the fish data are derived from continuous total body exposure. The latter conditions are not a very realistic model from which to assess the human hazard. Even chronic occupational exposures of men to hydrogen cyanide gas allows for respite at the end of each working day. No data were encountered which compared single acute oral LD_{50} doses in fish to ambient concentrations in their water which produced death within a specified interval.

Current Levels of Exposure

Since cyanide is encountered only infrequently in water supplies or in the atmosphere and since long-term and large-scale monitoring has not been carried out, insufficient

data exist to estimate current levels of exposure of the general population. A number of factors contribute to the rapid disappearance of cyanide from water. Bacteria and protozoa may degrade cyanide by converting it to carbon dioxide and ammonia (Leduc, et al. 1973). Cyanide is converted to cyanate during chlorination of water supplies (Rosehart and Chu, 1974). An alkaline pH favors the oxidation by chlorine, whereas an acid pH favors volatilization of HCN into the atmosphere. As cited, cyanide concentrations above 8 ppb were not found in a survey of 2,595 water samples collected throughout the United States (Towill, et al. 1978). Thus, these concentrations were well below the objective levels established by the PHS.

Special Groups at Risk

Although it was speculated that the elderly and the debilitated individuals in our population may be at special risk with respect to cyanide, no experimental or epidemiological studies can be cited to prove the point.

Basis and Derivation of Criterion

As shown in Table 4, the criterion of 0.2 mg CN^-/l allows for safety factors ranging from 41 to 2100. El Ghawabi, et al. (1975) studied the effects of chronic cyanide exposure in the electroplating sections of three Egyptian factories. A total of 36 male employees with exposures up to 15 years were studied and compared with a control group of 20 normal, non-smoking males. Only minimal differences with respect to thyroid gland size and function were found. The El Ghawabi study was given considerable weight in formulating the NIOSH

TABLE 4

Basis and Derivation of Cyanide Criterion

Exposure Levels[a]	Route	Species	Calculated Daily Exposure	Margin of Safety[d]	Investigator
9.2 mg/m^3	Inhalation	Man	60.8 mg[b]	152	El Ghawabi, et al. 1975
2.5 mg/m^3	Inhalation	Man	16.5 mg[b]	41	NIOSH, 1976
12 mg/kg	Oral	Rat	840 mg[c]	2100	Howard and Hanzal, 1955

[a] NOAEL

[b] Based on 100% retention and on alveolar exchange of $6.6m^3$ for 8 hours.

[c] Rat data converted to human equivalent assuming food consumption of 60 g/kg for rats and 70 kg human.

[d] Daily exposure compared with 0.4 mg/day exposure from the consumption of 2 l water containing 0.2 mg/l.

recommendations for occupational exposure which gives a safety factor of 41 when applied to drinking water by the usual extrapolations (Table 4). Finally, a safety factor of 2,100 is obtained using the results of a two year chronic feeding study in rats. When fed at the rate of 12 mg/kg per day over the equivalent of a lifetime, these rats showed no overt signs of cyanide poisoning, and hematological values were normal. Gross and microscopic examinations of tissues revealed no abnormalities. The only abnormality found was an elevation of thiocyanate levels in the liver and kidneys. Consequently the ADI for man is derived by taking the no observable adverse effect level in mammals (12 mg/kg/day) multiplied by the weight of the average man (70 kg) and dividing by a safety factor of 100. Thus,

ADI = 12 mg/kg/day x 70 kg ÷ 100 = 8.4 mg/day.

The equation for calculating the criterion for the cyanide content of water given an Acceptable Daily Intake is

$$2X + [(0.0187)\ (F)\ (X)] = ADI$$

Where

2 = amount of drinking water, l/day

X = cyanide concentration in water, mg/l

0.0187 = amount of fish consumed, kg/day

F = bioconcentration factor, mg cyanide/kg fish per mg cyanide/l water

ADI = limit on daily exposure for a 70 kg person = 8.4 mg/day

$$2X + (0.0187)\ (2.3)X = 8.4$$

$$X = 4.11 \text{ mg/l}$$

Thus, the current and recommended criteria (0.2 mg/l) has a margin of safety of 20.6 (4.11 ÷ 0.2).

No new additional evidence was encountered to suggest that the 1962 PHS Drinking Water Standard for cyanide should be lowered. The concentration of 0.2 mg/l or less is easily achieved by proper treatment and concentrations in excess of that amount have been encountered only on rare occasions in U.S. water supplies. The experience since 1962 suggests that 0.2 mg CN^-/l is a safe criterion for man.

REFERENCES

American Cyanamid Co. 1959. Report on sodium cyanide: 30-day repeated feedings to dogs. Central Med. Dep.

Braico, K.T., et al. 1979. Laetrile intoxication: Report of a fatal case. New England Jour.Med. 300: 238.

Brink, N.G., et al. 1950. Vitamin B_{12}: the identification of vitamin B_{12} as a cyano-cobalt coordination complex. Science 112: 354.

Brobeck, T.R. 1973. Best and Taylor's physiological basis of medical practice. 9th ed. Williams and Wilkins Co., Baltimore.

Chen, K.K., and C.L. Rose. 1952. Nitrite and thiosulfate therapy in cyanide poisoning. Jour. Am. Med. Assoc. 149: 113.

Conchie, J., et al. 1959. Mammalian glycosidases distribution in the body. Biochem. Jour. 71: 318.

Davison, V. 1969. Cyanide poisoning. Occup. Health 21: 306.

de Duve, C., et al. 1955. Tissue fractionation studies: 6. Intracellular distribution patterns of enzymes in rat-liver tissue. Biochem. Jour. 60: 604.

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Drinker, P. 1932. Hydrocyanic acid gas poisoning by absorption through the skin. Jour. Ind. Hyg. 14: 1.

Dudley, H.C., et al. 1942. Toxicology of acrylonitrile (vinyl cyanide): II. Studies of effects of daily inhalation. Jour. Ind. Hyg. Toxicol. 24: 255.

El Ghawabi, S.H., et al. 1975. Chronic cyanide exposure: a clinical, radioisotope, and laboratory study. Br. J. Ind. Med. 32: 215.

Fassett, D.W. 1963. Cyanides and nitriles. Page 1991 in D.W. FAssett and D.D. Irish, eds. Industrial hygiene and toxicology. Vol. 2. 2nd ed., John Wiley and Sons, Inc., New York.

Friedberg, K.D., and H.A. Schwarzkopf. 1969. Blausaureexhalation bei der Cyanidvergiftung (The exhalation of hydrocyanic acid in cyanide poisoning). Arch Toxicol. 24: 235.

Gettler, A.O., and A.V. St. George. 1934. Cyanide poisoning. Jour. Clin. Pathol. 4: 429.

Gosselin, R.E., et al. 1976. Clincial toxicity of commerical products. 4th ed. Williams and Wilkins Co., Baltimore.

Hayes, W.T. Jr. 1967. The 90-dose LD_{50} and a chronicity factor as measures of toxicity. Toxicol. Appl. Pharmacol. 11: 327.

Health and Welfare, Canada. 1977. Cyanide-drinking water criteria review. Draft document furnished by Dr. Peter Toft.

Hertting, G., et al. 1960. Untersuchungen uber die Folgen einer chronischen Verabreichung akut toxicher Dosen von Natriumcyanid an Hunden. Acta Pharmacol. Toxicol. 17: 27.

Heymans, C., and E. Neil. 1958. Cardiovascular reflexes of chemoreceptor origin. Page 176 in Reflexogenic areas of the cardiovascular system. J.A. Churchill, Ltd., London.

Himwich, W.A., and J.P. Saunders. 1948. Enzymatic conversion of cyanide to thiocyanate. Am. Jour. Physiol. 153: 348.

Howard, J.W., and R.F. Hanzal. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. Jour. Agric. Food Chem. 3: 325.

Hrizu, D., et al. 1973. Cytostatic effects of potassium sulfocyanate in vivo and in vitro. Arch. Roum. Pathol. Exp. Microbiol. 32: 155.

Johnstone, R.A.W., and J.R. Plimmer. 1959. The chemical constitutents of tobacco and tobacco smoke. Chem. Rev. 59: 885.

Kirk, R.L., and N.S. Stenhouse. 1953. Ability to smell solutions of potassium cyanide. Nature 171: 698.

Knowles, E.L., and J.T.B. Bain. 1968. Medical cover required in large scale production of cyanides and hydrocyanic acid. Chem. Ind. 8: 232.

Lawes, B.C. 1972. Control of cyanides in plating shop effluents: What's on the shelf now? Plating. 59: 394.

Leduc, G., et al. 1973. Use of sodium cyanide as a fish eradicant in some Quebec lakes. Natur. Can. 100: 1.

Lehninger, A.L. 1975. Biochemistry. 2nd ed. Worth Publishers, Inc., New York.

Lendle, L. 1964. Werkungsbedungungen von blausaure und schwefelwasserstoff und moglichreiten der vergiftungsbehandlung. Jap. Jour. Pharmacol. 14: 215.

McCabe, L.J., et al. 1970. Survey of community water supply systems. Jour. Am. Water Works Assoc. 62: 670.

McNerney, J.M., and H.H. Schrenk. 1960. The ac toxicity of cyanogen. Am. Ind. Hyg. Assoc. Jour. 21: 12.

Miller, L.P. 1973. Glycosides. Page 297 in Phytochemistry. Vol. I. Van Nostrand Reinhold Co. New York.

National Institute for Occupational Safety and Health. 1976. Criteria for recommended standard occupational exposure to hydrogen cyanide and cyanide salts (NaCN, KCN and $Ca(CN)_2$). NIOSH Publ. No. 77-108. Dep. Health Edu. Welfare. U.S. Government Printing Office, Washington, D.C.

Nicholls, P. 1975. The effect of sulfide on cytochrome aa_3. Isosteric and allosteric shifts of the reduced peak. Biochem. Biophys. Acta 396: 24.

Nowinski, W.W., and J. Pandra. 1946. Influence of sodium thiocyanate on the development of the chick embryo. Nature 157: 414.

Ortolani, G. 1969. The action of sodium thiocyanate (NaSCN) on the embryonic development of the ascidians. Acta Embryol. Exp. 27-34.

Osuntokun, B.O. 1968. An ataxic neuropathy in Nigeria. Brain 91: 215.

Ottinger, R.S., et al. 1973. Recommended methods for reduction, neutralization, recovery, or disposal of hazardous waste. Vol 1. EPA-670/2-73-053-a, U.S. Environ. Prot. Agency. U.S. Government Printing Office, Washington, D.C.

Perry, I.H. 1935. The effect of prolonged cyanide treatment on body and tumor growth in rats. Am. Jour. Cancer 25: 592.

Pettigrew, A.R., and G.S. Fell. 1973. Microdiffusion method for estimation of cyanide in whole blood and its application to the study of conversion of cyanide to thiocyanate. Clin. Chem. 19: 466.

Potter, A.L. 1950. The successful treatment of two recent cases of cyanide poisoning. Br. Jour. Ind. Med. 7: 125.

Prentiss, A.M. 1937. Systemic toxic agents. Page 170. in Chemicals in war. McGraw-Hill Book Co., Inc., New York.

Reed, A.K., et al. 1971. An investigation of techniques for removal of cyanide from electroplating wastes. Rep. No. 12010 EIE 11/71. U.S. Government Printing Office, Washington, D.C.

Rosehart, R.G., and R. Chu. 1974. Cyanide destruction in mine waste water. Water Pollut. Res. Can. 85.

Smith, L., et al. 1977. The effect of methemoglobin on the inhibition of cytochrome c oxidase by cyanide, sulfide or azide. Biochem. Pharmacol. 26: 2247.

Smith, R.P., and R.E. Gosselin. 1979. Hydrogen sulfide poisoning. Jour. Occup. Med. 21: 93.

Smith, R.P., and M.V. Olson. 1973. Drug-induced methemoglobinemia. Semin. Hematol. 10: 253.

Sorbo, B.H. 1953. On the substrate specificity of rhodanese. Acta Chem. Scand. 7: 32.

Terrill, J.B., et al. 1978. Toxic gases from fires. Science 200: 1343.

The Oak Ridger. 1975. State says cyanide caused lake fishkill. Oak Ridge, Tenn. September 5.

Tovo, S. 1955. Poisoning due to KCM absorbed through skin. Mineria Med. 75: 158.

Towill, L.E., et al. 1978. Reviews of the environmental effects of pollutants: V. Cyanide. Inf. Div. Oak Ridge Natl. Lab. Oak Ridge, Tenn.

U.S. Public Health Service. 1962. Drinking water standards. PHS Publ. No. 956. U.S. Government Printing Office, Washington, D.C.

Walton, D.C., and M.G. Witherspoon. 1926. Skin absorption of certain gases. Jour. Pharmacol. Exp. Ther. 26: 315.

Watson, M.R. 1973. Cyanide removal from water. Page 147. in Pollution control in metal finishing. Noges Data Corp., Park Ridge, N.J.

Way, J.L. et al. 1966. Effect of oxygen in cyanide intoxication: I. Prophylactic protection. Jour. Pharmacol. Exp. Ther. 153: 331.

Williams, R.T. 1959. Detoxication mechanisms. 2nd ed. John Wiley and Sons, Inc., New York.

Wilson, J., and D.M. Matthews. 1966. Metabolic interrelationships between cyanide, thiocyanate, and vitamin B_{12} in smokers and non-smokers. Clin. Sci. 31: 1.

Wolfsie, J. H., and C.B. Shaffer. 1959. Hydrogen cyanide. Jour. Occup. Med. 1: 281.

Wood, J.L., and S.L. Cooley. 1956. Detoxication of cyanide by cystine. Jour. Biol. Chem. 218: 449.